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Glassy Cell Carcinoma of the Uterine Cervix

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Background and Objectives: Glassy cell carcinoma (GCC) of the uterine cervix is a rare and highly malignant tumor, accounting for only 1%–2% of all cervical carcinomas. The purpose of this study was to investigate the clinical findings, treatment, and outcome of patients with cervical GCC in the south of Israel.

Methods: Data from the files of 5 patients with cervical GCC who were managed at the Soroka Medical Center, Beer-Sheva, Israel, between January 1961 and June 1999 were evaluated.

Results: Age at diagnosis ranged from 32 to 84 years, with 1 patient pregnant at the time of diagnosis. Vaginal bleeding was the prevailing presenting symptom. The cervical lesion was exophytic in 4 patients and endophytic ("barrel-shaped") in 1 patient. Mean tumor size was 3.9 cm. Three patients with stage IB_1 disease had radical hysterectomy and bilateral pelvic lymph node dissection followed by either external pelvic radiotherapy or brachytherapy or both. All 3 patients were alive without disease 4, 12, and 18 months after initial diagnosis, respectively. One patient with stage IIIB disease had external pelvic radiotherapy alone and died of disease 12 months after initial diagnosis. One patient with stage IVB disease refused treatment and died of disease 3 months after initial diagnosis.

Conclusions: Cervical GCC is a rare variant of cervical cancer with distinct histologic features and an alleged aggressive clinical behavior. For early-stage disease, the treatment of choice seems to be radical surgery followed by chemoradiotherapy.

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KEY WORDS: **adenosquamous carcinoma; vaginal bleeding; radical hysterectomy; pelvic radiotherapy; chemoradiotherapy; survival**

INTRODUCTION

Glassy cell carcinoma (GCC) of the uterine cervix is a rare and highly malignant tumor, accounting for only 1%–2% of all cervical carcinomas. It is typically composed of malignant cells having a moderate amount of cytoplasm with "ground glass" appearance, distinct cell membranes that stain with eosin or periodic acid–Schiff, and large nuclei with prominent nucleoli. Glucksmann and Cherry [1] first described this tumor in 1956 and regarded it as the most undifferentiated form of mixed glandular and squamous (adenosquamous) carcinoma of the uterine cervix, showing rapid clinical progression, frequent association with pregnancy, decreased response to radiotherapy, and poor outcome. It is estimated that since this original description, 200–250 cases of GCC of the uterine cervix have been listed in the literature [1–19].

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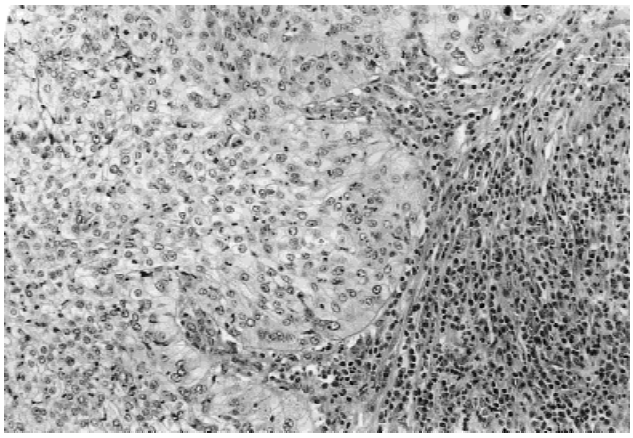

Fig. 1. Glassy cell carcinoma of the uterine cervix (case 1). Photomicrograph shows tumor composed of large malignant "glassy" cells with abundant amphophilic cytoplasm, distinct cell borders, large nuclei with prominent nucleoli, and numerous mitotic figures (left). The cervical stroma contains an intense infiltrate of plasma cells and eosinophils (right). Hematoxylin–eosin stain, original magnification ×200.

Because of the relative infrequency of cervical GCC, very few individuals or even referral centers can collect a large series of this tumor. This study presents the experience of the Soroka Medical Center, Beer-Sheva, Israel, and includes 5 patients with cervical GCC who were managed over a 39-year period. During this period, 446 cervical malignancies were diagnosed; thus, 5 cases of cervical GCC accounted for 1.1% of all cervical malignancies.

MATERIALS AND METHODS

The clinical and pathological records of 5 patients with GCC of the uterine cervix who were managed at the Soroka Medical Center, Beer-Sheva, Israel, between January 1961 and June 1999 were reviewed. The pathologic diagnosis of cervical GCC was based on accepted histologic criteria for GCC established in 1956 by Glucksmann and Cherry [1] and amplified in 1976 by Littman et al. [2]: moderate to large tumor cells (3–5 times the size of lymphocytes or neutrophils) with a finely granular "ground-glass" appearance of the cytoplasm, distinct cell borders, large and generally round nuclei, and prominent nucleoli. Multinucleated cells are occasionally present. Mitotic figures are numerous. Tumor cells are arranged in solid nests and groups separated by delicate thin connective tissue that is heavily infiltrated by inflammatory cells, predominantly eosinophils and plasma cells (Fig. 1). To be classified as GCC in this study, a glassy cell component had to occupy at least one-third of the tumor.

For patients who had surgery with radical hysterectomy and bilateral pelvic node dissection (RHND), the surgical technique performed was consistent with a class III extended hysterectomy as described by Piver et al. [20]. Pelvic lymph node dissection consisted of removal of all lymphatic tissue around the common, external, and internal iliac vessels and anterior to the obturator nerve. For patients who received external radiotherapy, it consisted of megavoltage photonic irradiation employing a 10 MeV linear accelerator delivering 4,500–7,020 cGy to the pelvis in daily fractions of 180 cGy via a 4-field box technique. For patients who received brachytherapy, it consisted of 2 vaginal intracavitary applications of brachytherapy, at a 2-week interval, using cesium-137 (each application 2,000–3,000 cGy to the vaginal vault) via an afterloading vaginal cylinder (Delclos).

After thorough record review, all patients were retrospectively staged according to the revised International Federation of Gynecology and Obstetrics (FIGO) staging system for gynecologic cancer [21].

The following data were retrieved from the files of the patients: ethnic origin, age at initial diagnosis, pre- or postmenopausal status, gravidity, parity, past medical history, associated diseases, presenting symptoms, time from the beginning of symptoms until seeking medical attention, tumor clinical appearance and size, stage of disease, treatment modality (primary and adjuvant), histopathologic findings (lymph node status, tumor size, fraction of cervical wall penetration, parametrial and paracervical tissue status, surgical margin status, and lymph/vascular space status), and results of follow-up.

RESULTS

The main clinical features, treatment, and outcome of the 5 cases are summarized in Table I. All 5 patients were Jewish; 3 were of Asian-African origin (Sephardic) and 2 were of European-American origin (Ashkenazi). The mean age at the time of diagnosis was 50.6 years (range 32–84). Four patients were premenopausal and 1 was postmenopausal. All patients were parous; the mean parity was 2.8 (range 1–8 children). One patient was pregnant (8-week gestation) at the time of diagnosis. Past medical history of the patients revealed that 1 patient had hypertension (blood pressure >140/90) and hypothyroidism and 1 patient had bronchial asthma. No patient had another primary cancer occurring either metachronously or synchronously with GCC of the uterine cervix.

In 4 patients abnormal vaginal bleeding was the presenting symptom, and in 1 patient the tumor was incidentally discovered during termination of an unwanted 8-week pregnancy. The time interval from the beginning of abnormal vaginal bleeding until seeking medical attention ranged from 2 weeks to 1 year (mean 4.1 months).

Four patients had an exophytic and friable tumor of the cervix and 1 had an endophytic tumor, forming a "barrel-shaped" cervix. The largest tumor diameter ranged from 3 to 6 cm (mean 3.9). In 3 patients the tumor was allocated FIGO stage IB_1 (tumor limited to the cervix and no

TABLE I. Clinical Features, Treatment, and Outcome in Glassy Cell Carcinoma of the Uterine Cervix (*n* = 5)

Case no., age (yr)/ gravidity and parity	Clinical presentation	Appearance	Stage	Treatment	Follow-up (months)/ outcome
Case 1 32/G3P1	Postcoital bleeding	Exophytic friable tumor, 3.5 × 1.5 cm	IB_1	RHND followed by external pelvic radiotherapy (4,500 cGy) and brachytherapy (4,000 cGy)	4/NED
Case 2 43/G2P1	Incidental finding during termination of pregnancy	Exophytic friable tumor, 2 × 3 cm	IB_1	RHND followed by external pelvic radiotherapy (4,500 cGy) and brachytherapy (4,000 cGy)	18/NED
Case 3 45/G7P1	Vaginal spotting	Exophytic friable tumor, 3 × 3 cm	IB_1	RHND followed by brachytherapy (6,000 cGy)	10/NED
Case 4 49/G8P8	Postcoital bleeding	Barrel-shaped cervix, 6 × 6 cm; extension onto anterior vaginal wall and both pelvic side walls	IIIB	External pelvic radiotherapy (7,020 cGy)	12/DOD
Case 5 84/G3P3	Vaginal bleeding	Exophytic friable tumor, 3 × 4 cm; extension onto left pelvic side wall; liver metastases	IVB	—	3/DOD

G, gravidity; P, parity; RHND, radical hysterectomy and bilateral pelvic lymph node dissection; NED, no evidence of disease; DOD, died of disease.

more than 4 cm in greatest dimension), in 1 patient the tumor was allocated FIGO stage IIIB (tumor extending onto pelvic side wall), and in 1 patient the tumor was allocated FIGO stage IVB (distant metastases). In all patients, biopsy of the cervical tumor established the diagnosis of GCC.

Three patients with stage IB_1 tumor (cases 1–3) had RHND as their primary treatment. The surgical–pathological data of these patients are detailed in Table II. All 3 patients received postoperative radiotherapy: 2 (cases 1 and 2) had external pelvic radiotherapy followed by 2 applications of brachytherapy and 1 (case 3) had 2 applications of brachytherapy alone. One patient with stage IIIB tumor (case 4) had external pelvic radiotherapy alone, and 1 patient with stage IVB disease (case 5) refused any treatment.

At the end of follow-up, the 3 patients with stage IB_1 disease who had radical surgery followed by radiotherapy were alive with no evidence of disease 4, 10, and 18 months after initial diagnosis, respectively. The patient with stage IIIB disease who had external pelvic radiotherapy alone died of disease 12 months after initial diagnosis, and the patient with stage IVB disease who refused treatment died of disease 3 months after initial diagnosis.

DISCUSSION

The presently reported 5 cases of GCC accounted for 1.1% of all cervical cancers seen during the study period. This finding corroborates previous studies that demonstrated that GCC accounts for 1%–2% of all cervical malignancies [1,2,4,8,9,12,15,17–19]. Although Arab-Bedouins make up nearly 20% of the population in southern Israel, not even a single case of cervical GCC was encountered among Arab-Bedouin women during the entire 39 years of the study period. The mean age at the time of diagnosis was 50.6 years. If the 84-year-old patient (case 5) is excluded, the mean age drops to 42.2 (range 32–49 years). This is in accord with previous studies that demonstrated that the mean age of patients with GCC (41 years) is 10 years younger than that of patients with other cervical cancers (51 years) [7,9,12,15,18]. An association between cervical GCC and pregnancy was recorded in 2 studies [1,4], and 4 other reports, including the present one, contain a single pregnant patient [7,10,16]. It has, however, been concluded that the seemingly higher association of cervical GCC with pregnancy is merely a reflection of the relatively younger age of women with this tumor [7].

The most common clinical symptom is vaginal bleeding, notably postcoital bleeding. In this report, 4 tumors (cases 1–3 and 5) were defined as exophytic and friable and 1 tumor (case 4) was defined as bulky, forming a "barrel-shaped" cervix. In 1 patient (case 1), despite a 3.5 × 1.5 cm exophytic and friable tumor located on the exocervix, there was only superficial invasion (1–2 mm) of the cervical stroma. This finding corroborates previous studies that demonstrated that the gross appearance of most GCCs is that of a large exophytic and friable tumor. In some cases, despite large tumor volume, there is only superficial invasion, generally less than the inner third of the cervical stroma [12,15].

The majority of patients with GCC of the cervix are clinically diagnosed with FIGO stage IB disease. How-

TABLE II. Surgical–Pathological Data of Patients Who Had Radical Hysterectomy and Bilateral Pelvic Lymph Node Dissection for Glassy Cell Carcinoma of the Uterine Cervix (*n* = 3)

Variable	Case 1	Case 2	Case 3
Number of positive pelvic lymph nodes/total number of pelvic lymph nodes removed	1/34	0/46	0/23
Tumor's greatest dimension on pathological examination, cm	3.5	2.6	5
Fraction of cervical wall penetration	Tumor on surface of exocervix, superficially (1–2 mm) penetrating stroma	>50%	>50%
Parametrial involvement	—	—	—
Paracervical involvement	—	—	—
Close or involved vaginal margins	—	—	—
Close or involved other surgical margins	—	—	—
Lymph/vascular space invasion	—	—	+
Uterine involvement	—	+	—

ever, in many of these patients, the tumor is clinically understaged [12]. In the present report, in only 1 patient (case 1) was the surgical stage more advanced than the clinical stage; although the tumor only superficially invaded (1–2 mm) the cervical stroma, 1 of 34 pelvic lymph nodes was positive for metastases. This case confirms the established reputation of GCC of the cervix as a rapidly progressive and biologically aggressive tumor with early metastasis [1–19]. Some authors, however, have claimed that since GCC of the uterine cervix is often clinically understaged, it is usually not properly treated rather than being less sensitive to treatment as previously described [12].

Glucksman and Cherry [1], who first described cervical GCC in 1956, and other authors [7,9,15,17] have regarded this tumor as the most undifferentiated form of adenosquamous carcinoma rather than a distinct clinicopathologic entity. Some authors [12,14,18], however, have suggested that cervical GCC is a separate and distinct clinicopathologic entity. Costa et al. [17] have divided adenocarcinoma of the uterine cervix into the following histologic subtypes: pure adenocarcinoma, adenosquamous carcinoma with no glassy cell features, and adenosquamous carcinoma with glassy cell features. Adenosquamous carcinoma with glassy cell features may be further divided into adenosquamous carcinoma with predominant glassy cell features (>85% of histology) and adenosquamous carcinoma with focal glassy cell features (33%–85% of histology) [17]. Although the histologic criteria for the diagnosis of GCC have been established for >40 years, this tumor is still most likely to be confused with adenosquamous carcinoma, poorly differentiated large cell nonkeratinizing squamous cell carcinoma, and undifferentiated carcinoma of the uterine cervix [12].

It has traditionally been reiterated that despite aggressive treatment, including radical surgery, radiotherapy and chemotherapy, the survival of patients with GCC of the uterine cervix is worse than that of patients with other cervical carcinomas [1,2,10–12,15]. The 5-year survival of patients with stage IB GCC of the cervix was 45% when treated with primary radical surgery in contrast to 90% for squamous cell carcinoma and 78% for adenocarcionoma [18]. When bimodal therapy with radical surgery and radical radiotherapy was used, the survival of patients with stage IB GCC improved to 87%. Survival of patients with stage II GCC of the cervix improved from 50% to 85% with combined radical surgery and radiotherapy [18]. On the other hand, the survival data of patients with GCC, undifferentiated carcinoma, poorly differentiated large cell nonkeratinizing squamous cell carcinoma, and adenocarcinoma of the uterine cervix have been shown to be about equal for the same stages. Thus, it has been postulated that the poor survival of patients with GCC may reflect clinical understaging rather than unresponsiveness to treatment [9,12]. The number of cases of GCC of the uterine cervix is unfortunately too small to draw conclusions about treatment of choice and survival. It seems, however, that for early-stage disease (stages IA_2, IB and IIA) the treatment of choice is primary surgery with RHND followed by pelvic radiotherapy (with or without para-aortic extension). For advanced-stage disease (stage IIB and more), treatment includes radiotherapy alone.

A controversial issue is the preservation of the patient's ovaries during radical surgery for early-stage GCC of the uterine cervix. In contrast to cervical squamous cell carcinoma, in which ovarian metastases have been detected in no more than 0.5% of cases, in cervical adenocarcinoma microscopic ovarian metastases have been noticed in up to 7% of cases. Thus, preservation of the ovaries in young patients with early-stage cervical adenocarcinoma has been a subject of debate [22]. There are only 2 documented cases of ovarian metastasis with GCC: Nahhas et al. [3] reported on a patient with a clinical stage IB GCC of the cervix with ovarian metastases and Reisinger et al. [16] encountered a case of recurrent carcinoma in a transposed ovary in a patient with stage IB GCC of the cervix who was pregnant when

the cervical tumor was first diagnosed. Ovarian conservation may not be advisable in patients with GCC due to the aggressive nature of the tumor.

It has been demonstrated that addition of cisplatin-containing chemotherapy to pelvic radiotherapy decreases the risk of dying from high-risk cervical cancer by 30%–50% [23–27]. Thus, it is highly recommended that whenever pelvic radiotherapy is planned for cervical GCC, it should concurrently be given with cisplatin-containing systemic chemotherapy (chemoradiotherapy).

In conclusion, cervical GCC is a rare tumor, accounting for only 1%–2% of all cervical malignancies. Histologically, the tumor is composed of typical "glassy cells" arranged in nests separated by connective tissue septa infiltrated by eosinophils and plasma cells. Clinically, GCC has a reputation of being an aggressive tumor with early metastasis and poor outcome. Most authors have regarded GCC as the most undifferentiated form of adenosquamous carcinoma, whereas others have considered it a separate and distinct clinicopathologic entity. The most common presenting symptom is vaginal bleeding, notably postcoital bleeding. It usually affects premenopausal women and is most often diagnosed in an early clinical stage. In many cases, however, the surgical stage is more advanced than the clinical stage. The number of cases of cervical GCC is too small to draw conclusions about the treatment of choice and survival. It seems, however, that for early-stage disease (stages IA_2, IB and IIA) the treatment of choice should include primary surgery with RHND followed by pelvic radiotherapy (with or without para-aortic extension) given concurrently with cisplatin-containing systemic chemotherapy (chemoradiotherapy). For advanced-stage disease (stage IIB and greater), treatment should include chemoradiotherapy alone.

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